CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
FERROUS SULFATE

Chemical Code # 000289, Tolerance # 50761
SB 950 # 684
12/17/02

I. DATA GAP STATUS

Chronic toxicity, rat:	Data gap, no study submitted.
Chronic toxicity, dog:	Data gap, no study submitted
Oncogenicity, rat:	Data gap, no study submitted
Oncogenicity, mouse:	Data gap, no study submitted
Reproduction, rat:	Data gap, no study submitted.
Teratology, rat:	Data gap, inadequate study, no adverse effect indicated.
Teratology, mouse:	Data gap, inadequate study, no adverse effect indicated.
Teratology, rabbit:	Data gap, no study submitted.
Gene mutation:	Data gap, inadequate study, possible adverse effect indicated
Chromosome effects:	Data gap, no study submitted
DNA damage:	Data gap, inadequate study, possible adverse effect indicated
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.
All record numbers through 041185 were examined.
** Indicates an acceptable study.
Bold face indicates a possible adverse effect.
File name: T021217
Original: Kishiyama and Gee, 12/17/02

Ferrous sulfate is a GRAS-listed chemical. The data requirements under SB950 have been waived for ferrous sulfate with the concurrence with OEHHA. See memorandum of November 7, 1995, from Anna M. Fan, Chief, Pesticide and Environmental Toxicology, OEHHA, to Barry Cortez, Chief, Pesticide Registration Branch, DPR.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

CHRONIC TOXICITY, RAT

No study submitted.

CHRONIC TOXICITY, DOG

No study submitted.

ONCOGENICITY, RAT

No study submitted.

ONCOGENICITY, MOUSE

No study submitted.

REPRODUCTION, RAT

No study submitted.

TERATOLOGY, RAT

50761 - 001 041183 Bailey, D. E. and K. Morgareidge. "Teratologic Evaluation of FDA 71-64, Ferrous Sulfate in Mice and Rats." (Food and Drug Research Laboratories, Incorporated, Laboratory No. 2143(19), November 15, 1974.) FDA 71-64 (ferrous sulfate, purity not stated) was administered via gavage at doses of 0, 2.0, 9.3, 43.1 or 200 mg/kg, days 6 through 15 of gestation, to 21 – 25 mated female Wistar rats/group. Aspirin (250 mg/kg/day) was the positive control. No treatment-related effects reported. Aspirin exposure resulted in positive findings on the fetus. Maternal and developmental NOEL $\geq$ 200 mg/kg/day. UNACCEPTABLE (numerous deficiencies including dose selection). Not upgradeable. (Kishiyama and Gee, 12/13/02).

TERATOLOGY, MOUSE

50761 - 001 041182 Bailey, D.E. and K. Morgareidge. "Teratologic Evaluation of FDA 71-64, Ferrous Sulfate in Mice and Rats." (Food and Drug Research Laboratories, Incorporated, Laboratory No. 2123 (19), November 15, 1974." FDA 71-64 (ferrous sulfate, purity not stated) was administered via gavage at doses of 0, 1.6, 7.4, 34.5 or 160 mg/kg, during days 6 through 15 of gestation, to 22 – 28 mated female CD-1 mice/group. Aspirin (150 mg/kg) was used as the positive control. No treatment-related effects reported on dams or fetuses. Maternal and developmental NOEL $\geq$ 160 mg/kg/day. UNACCEPTABLE (doses not justified, many others). (Kishiyama and Gee, 12/12/02).

TERATOLOGY, RABBIT

No study submitted.

GENE MUTATION

50761 - 001 041184 Brusick, D. "Mutagenic Evaluation of Compound FDA 71-64, Ferrous Sulfate." (Litton Bionetics, Incorporated, Project No. 02468, Contract No. 223-74-2104, October 29, 1974.) FDA 71-64 (ferrous sulfate, purity not stated) was evaluated for mutagenicity at a concentration of 0 and 0.50% without and with metabolic activation (S9 Mix) using *Salmonella typhimurium* strains TA 1535, TA 1537, and TA 1538. Homogenates from liver, lung, and testes tissues of adult male random bred mice, Sprague-Dawley rats, and monkeys (*Macaca mulatta)* were compared for activity using plate incorporation and suspensions tests. Suspension tests indicated an increase in revertants with liver compared to lung or testes homogenates and greater when obtained from rats rather than mouse and monkey. **FDA 71-64 plus rat liver homogenate increased the number of revertants in TA1537 during the initial and repeat suspension tests and, to a lesser extent, with TA1538** (frameshift mutants)**.** UNACCEPTABLE. (major deficiencies). Not upgradeable. (Kishiyama and Gee, 12/13/02).

CHROMOSOME EFFECTS

No study submitted.

DNA DAMAGE

50761 - 001 041184 Brusick, D. "Mutagenic Evaluation of Compound FDA 71-64, Ferrous Sulfate." (Litton Bionetics, Incorporated, Project No. 02468, Contract No. 223-74-2104, October 29, 1974.) FDA 71-64 (ferrous sulfate, purity not stated) was evaluated for mutagenicity at a concentration of 0.50% without and with metabolic activation (S9 Mix) using *Saccharomyces cerevisae* Strain D4 . Homogenates from the liver, lung, and testis tissues of adult male random bred mice, Sprague-Dawley rats, and monkeys (*Macaca mulatta)* were compared for activity. Increased gene conversion at both tryptophan and adenine loci were observed with mouse liver, rat lung, and monkey liver, lung and testes homogenates. UNACCEPTABLE. (major deficiencies). Possible adverse effect. (Kishiyama and Gee, 12/13/02).

NEUROTOXICITY

Not required at this time.

OTHER

50761 - 001 041185 Verrett, M. J. "Investigations of the toxic and teratogenic effects of GRAS substances to the developing chicken embryo: Ferrous sulfate." (Food and Drug Administration, 1973) Ferrous sulfate (lot WZPV, purity not stated) was administered in water using four sets of conditions. Two routes (air sac and yolk) and two stages (0 hours and 96 hours) were used with several dose levels per condition. Fifteen or more eggs were treated per group. Eggs were candled daily and non-viable embryos removed. Surviving embryos were allowed to hatch and chicks were examined for external and internal abnormalities as well as edema and hemorrhage. Doses used ranged from 0 (water), 0 (untreated), 0.05, 0.125, 0.250, 0.5, 1.25 and 2.5 mg/egg. Doses were also expressed as mg/kg based on 50 g/egg. In all cases, the number of eggs treated was 45 or higher. In general, mortality increased with increasing dose in all sets. There was no consistent increase in total number of abnormal birds or in the number with structural abnormalities. The conclusion was that ferrous sulfate did not cause teratogenic effects but did causes statistically significant increases in mortality under test conditions. Supplemental study. (Gee, 12/16/02)